

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 10 NOV 2005

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Applicant's or agent's file reference PC503PR		FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2004/006330		International filing date (day/month/year) 11.06.2004	Priority date (day/month/year) 13.06.2003	
International Patent Classification (IPC) or national classification and IPC C07C235/52, C07D333/08, C07D209/04, C07D241/40, C07D213/02, A61K31/166, A61K31/381, A61K31/404, A61K31/498, A61K31/435, A61P5/00				
Applicant LABORATORIOS S.A.L.V.A.T., S.A. et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 21 sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 13.04.2005		Date of completion of this report 08.11.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Goetz, G Telephone No. +49 89 2399-8105		

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/006330

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-4, 7, 9, 10, 12-16, 19-83, 85-90	as originally filed
5, 5a, 6, 8, 11, 17, 18, 84	received on 15.04.2005 with letter of 13.04.2005

Claims, Numbers

9-38	as originally filed
1-8	received on 15.04.2005 with letter of 13.04.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☒ the claims, Nos. 1
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/006330

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 30-38

because:

- ☒ the said international application, or the said claims Nos. 30-38 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- ☐ has not been furnished

- ☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished

- ☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-38
	No: Claims	
Inventive step (IS)	Yes: Claims	1-38
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/006330

D1: WO 00/55118 A (GLAXO GROUP LTD ; BLANCHARD STEVEN GERARD (US); COBB JEFFERY EDMUND (U) 21 September 2000 (2000-09-21)
D2: WO 97/27847 A (PATCHETT ARTHUR A ; BERGER JOEL P (US); MERCK & CO INC (US); MOLLER DA) 7 August 1997 (1997-08-07)

1. For the assessment of the present claims 30 to 38 on the question whether they are industrially-applicable, ~~no unified criteria exist in the PCT Contracting States. The~~ patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 30 - 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Following amendments are considered to go beyond the disclosure as originally filed (Article 34(2)(b) PCT:

Definition of -I'- :

The added substituents "phenyl", "phenoxy" and "benzyloxy" have their basis only in the examples, where other variables have a certain specific definition.

Any generalization of the examples is considered to represent an amendment which violates the requirements of Article 34(2)(b) PCT.

Definition of R6 and R7:

Basis for this amendment is to be found only in examples 36 and 251. Any generalization of the examples is considered to represent an amendment which violates the requirements of Article 34(2)(b) PCT.

The present International Preliminary Examination Report is thus based on claim 1 as originally filed.

3. The claimed compounds differ from the compounds disclosed in D1 by the fact that in D1 the phenyl-ring of the benzamid-group is substituted by a nitro group and a group "X" whereas the claimed compounds do not have such a substitution pattern. The claimed compounds differ from the compounds disclosed in D2 by the fact that D2 does not disclose benzamid-derivatives. The subject matter of present claims 1 to 38 is thus considered to be novel over said prior art (PCT Article 33.2).

4. In view of D1 which is considered to represent the closest prior art the underlying problem can be defined by the provision of further compounds acting as modulators of PPAR-gamma.

To represent a solution it has to be shown that a representative amount of compounds falling within the scope of present formula (I) but showing different structural features show this activity. In particular a representative number of benzamides falling within the structure of formula (I) but having different substitution pattern have to be tested and proven for their activity.

Having regard to the data provided by the Applicant (see Annex I) it can be considered that the underlying problem has been solved over the whole scope of the general formula (I) of claim 1.

This solution is in addition considered to be based on an inventive step: starting from D1 as the closest prior art document it was not obvious for the skilled person to modify the basic structure of the compounds of D1 in the way it has been done in present application to still get biological active modulators of PPAR-gamma.

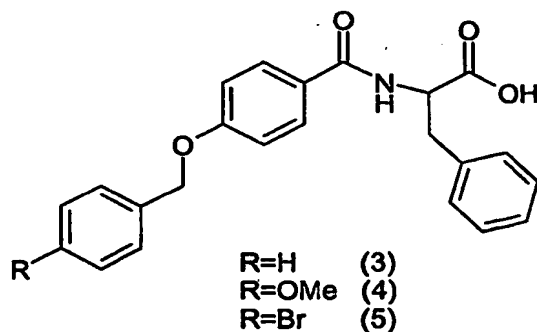
Consequently present claims 1 to 38 are considered to be based on an inventive step (PCT Article 33.3).

5. Industrial applicability is given for present claims 1 to 29 (PCT Article 33.3).

discovery of drugs that have great potential in the treatment of diseases such as type-2 diabetes, dyslipidemia, syndrome X, cardiovascular diseases (including atherosclerosis), hypercholesteremia, colon cancer, skin disorders (including psoriasis, and wound healing, Tan et al., *Expert Opin. Ther. Targets*, 2004, 8, 39), and bone diseases (Pei et al., *J. Clin. Invest.*, 2004, 113, 805-806).

Consequently, it is of great interest to provide new therapeutic agents that selectively modulate PPAR γ , and PPAR γ / PPAR δ .

Kundu and collaborators have described benzamides (3), (4) and (5) as N- α -glucosidase inhibitors (*Comb. Chem. High.* 2002, 5, 545-550). These compounds are structurally close to those of this invention, but were described for different uses.

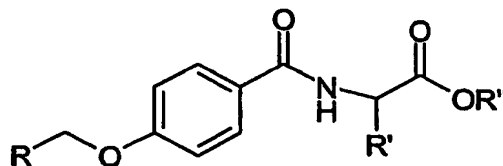


Kundu and collaborators have described benzamides (3), (4) and (5) as N- α -glucosidase inhibitors (*Comb. Chem. High.* 2002, 5, 545-550). WO 02/096426 disclose compounds (6) and (7) as intermediates for compounds which are matrix metalloproteinase inhibitors. Finally, WO 04/014844 disclose compounds (8) and (9) as factor IX modulators. These

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compounds are structurally close to those of this invention, but were described for different uses.



<u>R</u>	<u>R'</u>	<u>R''</u>
(3) Phenyl-	Benzyl-	-H
(4) 4-Methoxyphenyl-	Benzyl-	-H
(5) 4-Bromophenyl-	Benzyl-	-H
(6) 2-Methylquinolin-4-yl-	Cyclopentyl-	-methyl
(7) 2-Methylquinolin-4-yl-	Tetrahydropyran-4-yl-	-methyl
(8) Phenyl-	Biphenyl-4-ylmethyl	-H
(9) Phenyl-	4'-Trifluoromethoxybiphenyl-4-methyl-	-H

SUMMARY OF THE INVENTION

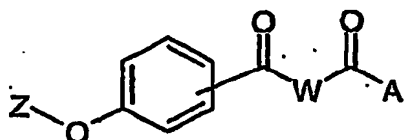
One aspect of the present invention relates to the provision of new compounds of formula (I),

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(I)

its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein the central benzene ring may be substituted in meta- or para-position and,

-A is a radical selected from the group consisting of -OR₁, -NR₂OR₁ and -NR₂R₃; wherein R₁, R₂ and R₃ independently represent -H or -(C₁-C₄)-alkyl;

-W- is a biradical selected from the group: -NH-CH(E)-, -N(E)-CH₂-, and -N(D)-CH₂-CH₂-; wherein E is a radical of the -G-I-J-K type and D is a radical of the -G-I'-J-K type where:

-G - is a bond or a -(CH₂)₁₋₄- biradical;

-I - is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphanyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -

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being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphiny, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-J- is a bond or a biradical selected from the following groups:

a) - (CH₂)₁₋₄-alkylidene;

b) ~~-O-, -S-, -SO-, -SO₂-, -CO-, -OCO-, -COO-,~~
~~-OCONR₂-, -NR₂COO-, -CONR₂-, -NR₂CO-, -NR₂-,~~
~~-NR₂CO-, -SO₂NR₂-, and~~

c) $-O-(C_1-C_4)-$ ~~$-(C_1-C_4)-O-$, $-S(C_1-C_4)-$, $(C_1-C_4)-S-$, $-SO-(C_1-C_4)-$, $-(C_1-C_4)-SO-$, $-SO_2-(C_1-C_4)-$, $-(C_1-C_4)-SO_2-$, $-OCO-(C_1-C_4)-$, $-COO-(C_1-C_4)-$, $-(C_1-C_4)-OCO-$, $-(C_1-C_4)-COO-$, $-OCONR_2-(C_1-C_4)-$, $-NR_2COO-(C_1-C_4)-$, $-(C_1-C_4)-OCONR_2-$, $-(C_1-C_4)-NR_2COO-$, $-CONR_2-(C_1-C_4)-$, $-NR_2CO-(C_1-C_4)-$, $-(C_1-C_4)-CONR_2-$, $-(C_1-C_4)-NR_2CO-$, $-NR_2-(C_1-C_4)-$, $-(C_1-C_4)-NR_2-$, $-SO_2NR_2-(C_1-C_4)-$, $-NR_2SO_2-(C_1-C_4)-$, $-(C_1-C_4)-SO_2NR_2-$, $-(C_1-C_4)-NR_2SO_2-$~~

-K is a radical selected from the following groups:

a) -H;

b) (C₁-C₄)-alkyl;

c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all

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c) benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃,

(C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, ~~and~~ (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F, phenyl, phenoxy and benzyloxy;

-Z is a radical selected from the following groups:

a) -Q-I-J-T wherein

-Q- is a biradical -(CH₂)₁₋₃-;

-I- is as defined above;

-J- is as defined above; and

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optionally substituted by one or several
-OH or -F, and (C₁-C₄)-alkoxyl optionally
substituted by one or several -OH or -F;
and

c.e) a heterocycle and
heterocycle-(C₁-C₃)-alkyl, wherein the
heterocycle is a five- or six-membered
ring containing from one to three
heteroatoms selected from O, S and N,
being this heterocycle optionally
substituted by one or several radicals
selected from -OH, oxo (=O), -CHO, -SH,
-NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl,
(C₁-C₄)-alkoxycarbonyl,
(C₁-C₄)-alkanoyloxy,
(C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl
optionally substituted by one or
several -OH or -F, and
(C₁-C₄)-alkoxyl optionally substituted by
one or several -OH or -F;

-P- is as defined above;

-I- is as defined above;

-J- is as defined above; and

-T is as defined above;

d) -(CH₂)_s-NR₆R₇, wherein s is as defined above,
and R₆ and R₇ together with the N are joined
forming a five-, ~~six-membered~~ ^{or seven-membered} cycle
optionally containing from one to three
additional heteroatoms selected from O, S and

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N, and that may be fused or substituted by one or two five- or six-membered cycles optionally containing one or several heteroatoms selected from the group composed of O, S and N, all the cycles being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F; and

- e) -(CH₂)_u-CO-NR₆R₇ wherein u is as defined above, and R₆ and R₇ are as defined above;

with the proviso that compound of formula (I) is neither of
 2-(4-benzyloxybenzoylamino)-3-phenylpropionic acid, ~~nor~~
 2-[4-(4-methoxybenzyloxy)benzoylamino]-3-phenylpropionic
 acid, ~~nor~~
 2-[4-(4-bromobenzyloxy)benzoylamino]-3-phenylpropionic acid,
 insert (-) from page 103.

In a particular embodiment of this aspect of the invention, in the compounds of formula (I), -W- is -NH-CH(E)-. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -Q-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -(CH₂)₅-X-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -(CH₂)₅-O-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -(CH₂)₂-NR₄-P-I-J-T type. In another

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260	3-(4-Benzyloxyphenyl)-2-{4-[(phenylpyridin-2-yl-carbamoyl)methoxy]-benzoylamino}propionic acid; ¹ H-NMR: 9.92 (d, 1H), 7.62-7.40 (m, 6H), 7.35 (d, 2H), 7.30-7.10 (m, 7H), 7.12 (d, 1H), 6.97 (d, 2H), 6.90 (2H), 6.75 (d, 2H), 5.27 (s, 2H), 4.89 (s 2H), 4.76 (t, 1H), 3.11 (dd, 1H), 3.01 (dd, 1H)
261	3-(4-Benzyloxyphenyl)-2-{4-[(cyclohexylphenylcarbamoyl)methoxy]-benzoylamino}propionic acid; MS: 607
262	3-(4-Benzyloxyphenyl)-2-{4-[(<i>tert</i> -butylcyclohexylcarbamoyl)methoxy]-benzoylamino}propionic acid; MS: 587
263	3-(4-Benzyloxyphenyl)-2-(4-{[(2-fluorophenyl)thiophen-2-ylmethylcarbamoyl]methoxy}benzoylamino)propionic acid; MS: 639
264	(2 <i>S</i>)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methyl-2-oxo-2 <i>H</i> -quinoxalin-1-yl)ethoxy]benzoylamino}propionic acid; MS: 578
265	(2 <i>S</i>)-3-((4-Benzyloxybenzyl)-{3-[2-(3-methyl-2-oxo-2 <i>H</i> -quinoxalin-1-yl)ethoxy]benzoyl}amino)propionic acid; MS: 592

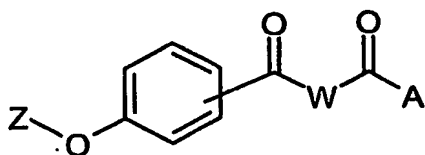
EXAMPLES (Ic) and (Id)

The compounds of formula (Ic) and (Id) shown in Table 18 were synthesized either according to any of methods A to C, starting from compounds of formula (Ib) and the aminic derivatives HNR₂R₃ or HNR₂OR₁:

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CLAIMS

1. A compound of formula (I),



(I)

its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein the central benzene ring may be substituted in meta- or para-position and,

-A is a radical selected from the group consisting of -OR₁, -NR₂OR₁ and -NR₂R₃; wherein R₁, R₂ and R₃ independently represent -H or -(C₁-C₄)-alkyl;

-W- is a biradical selected from the group: -NH-CH(E)-, and -N(D)-CH₂-CH₂-; wherein E is a radical of the -G-I-J-K type and D is a radical of the -G-I'-J-K type where:

-G- is a bond or a -(CH₂)₁₋₄- biradical;

-I- is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br,

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(C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl,
 (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl,
 (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl,
 (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
 -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
 substituted by one or several -OH or -F, and
 (C₁-C₄)-alkoxyl optionally substituted by one
 or several -OH or -F;

- b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, this heterocycle being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;
- c) benzene or benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F; and

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d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, this bicyclic system being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-J- is a bond or a biradical selected from the following groups:

- a) -(CH₂)₁₋₄-alkylidene;
- b) -O-, and
- c) -O-(C₁-C₄)-alkyl-;

-K is a radical selected from the following groups:

- a) -H;
- b) (C₁-C₄)-alkyl;
- c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all of them optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,

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-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

d) a radical from a five- or six-membered heterocycle containing from one to three heteroatoms selected from O, S and N, being ~~this heterocycle optionally substituted by one~~

or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F; and

e) phenyl or phenyl optionally substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-I'- is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally

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substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
~~NR₂R₃, CONR₂R₃, (C₁-C₄)-alkyl optionally~~

substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
~~NR₂R₃, CONR₂R₃, (C₁-C₄)-alkyl optionally~~
substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

c) benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
~~NR₂R₃, CONR₂R₃, (C₁-C₄)-alkyl optionally~~
substituted by one or

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several -OH or -F, (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F phenyl, phenoxy and benzyloxy; and

- d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-Z is a radical selected from the following groups:

- a) -Q-I-J-T wherein

-Q- is a biradical -(CH₂)₁₋₃-;

-I- is as defined above;

-J- is as defined above; and

-T is a radical selected from the following groups:

a.a) -H;

a.b) (C₁-C₄)-alkyl;

a.c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all of them optionally substituted by one or several radicals independently selected

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from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN,
-F, -Cl, -Br, (C₁-C₄)-alkanoyl,
(C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy,
(C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
~~NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally~~

substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F;

a.d) a radical from a five- or six-membered
heterocycle containing from one to three
heteroatoms selected from O, S and N, this
heterocycle being optionally substituted by
one or several radicals independently
selected from -OH, oxo (=O), -CHO, -SH,
-NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl,
(C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy,
(C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
~~NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally~~
substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F;

a.e) phenyl or phenyl optionally substituted
by one or several radicals independently
selected from -OH, -CHO, -SH, -NO₂, -CN,
-F, -Cl, -Br, (C₁-C₄)-alkanoyl,
(C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy,
(C₁-C₄)-alkylsulphinyl,

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(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F; and

~~a.f)~~ a radical from a bicyclic system

consisting of a benzene fused with a five-
or six-membered ring optionally containing
from one to three heteroatoms selected from
O, S and N, being this bicyclic system
optionally substituted by one or several
radicals independently selected from -OH,
oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl,
-Br, (C₁-C₄)-alkanoyl,
(C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy,
(C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F;

b) -(CH₂)_s-X-P-I-J-T wherein

s is 2 or 3;

-X- is selected from the group consisting of -O-,
-S-, -SO-, -SO₂- and -NR₄-, being R₄ a radical
selected from the group:

b.a) -H;

b.b) (C₁-C₁₀)-alkyl;

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b.c) cycloalkyl, cycloalkyl-CO-,
 cycloalkyl-(C₁-C₃)-alkyl and
 cycloalkyl-(C₁-C₃)-alkanoyl, wherein the
 cycloalkyl is a five- or six-membered ring
 optionally substituted by one or several
 radicals selected from -OH, oxo (=O), -CHO,
 -SH, -NO₂, -CN, -F, -Cl, -Br,
 (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl,
 (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl,
 (C₁-C₄)-alkylsulphenyl,
 (C₁-C₄)-alkylsulphonyl,
 (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
 -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
 substituted by one or several -OH or -F,
 and -(C₁-C₄)-alkoxyl optionally substituted
 by one or several OH or F;

b.d) phenyl, phenyl-CO-, phenyl-(C₁-C₃)-alkyl
 and phenyl-(C₁-C₃)-alkanoyl, being this
 aromatic ring optionally substituted by one
 or several radicals selected from -OH,
 -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br,
 (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl,
 (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl,
 (C₁-C₄)-alkylsulphenyl,
 (C₁-C₄)-alkylsulphonyl,
 (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
 -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
 substituted by one or several -OH or -F,
 and (C₁-C₄)-alkoxyl optionally substituted
 by one or several -OH or -F; and

b.e) a heterocycle, heterocycle-CO-,
 heterocycle-(C₁-C₃)-alkyl and
 heterocycle-(C₁-C₃)-alkanoyl, wherein the

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heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is a bond or a -(CH₂)₁₋₄- biradical;

-I- is as defined above;

-J- is as defined above; and

-T is a radical as defined above;

c) -(CH₂)_u-CO-NR₅-P-I-J-T wherein

u is 1 or 2;

-R₅ is a radical selected from the group:

c.a) -H;

c.b) (C₁-C₁₀)-alkyl;

c.c) cycloalkyl and cycloalkyl-(C₁-C₃)-alkyl, wherein the cycloalkyl is a five- or six-membered ring optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl,

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(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F;

c.d) phenyl and phenyl-(C₁-C₃)-alkyl, being
this aromatic ring optionally substituted
by one or several radicals selected from
-OH, -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br,
(C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl,
(C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally
substituted by one or several -OH or -F,
and (C₁-C₄)-alkoxyl optionally substituted
by one or several -OH or -F; and

c.e) a heterocycle and
heterocycle-(C₁-C₃)-alkyl, wherein the
heterocycle is a five- or six-membered ring
containing from one to three heteroatoms
selected from O, S and N, being this
heterocycle optionally substituted by one
or several radicals selected from -OH, oxo
(=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br,
(C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl,
(C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl,
(C₁-C₄)-alkylsulphenyl,
(C₁-C₄)-alkylsulphonyl,
(C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-,
-NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally

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substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is as defined above;

-I- is as defined above;

-J- is as defined above; and

-T is as defined above;

- d) ~~-(CH₂)_s-NR₆R₇, wherein s is as defined above, and~~
 R₆ and R₇ together with the N are joined forming a five-, six, or seven-membered cycle optionally containing from one to three additional heteroatoms selected from O, S and N, and that may be fused or substituted by one or two five- or six-membered cycles optionally containing one or several heteroatoms selected from the group composed of O, S and N, all the cycles being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO₂, -CN, -F, -Cl, -Br, (C₁-C₄)-alkanoyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkanoyloxy, (C₁-C₄)-alkylsulphinyl, (C₁-C₄)-alkylsulphenyl, (C₁-C₄)-alkylsulphonyl, (C₁-C₄)-alkyloxy-SO₂-, (C₁-C₄)-alkyl-SO₂O-, -NR₂R₃, -CONR₂R₃, (C₁-C₄)-alkyl optionally substituted by one or several -OH or -F, and (C₁-C₄)-alkoxyl optionally substituted by one or several -OH or -F; and
- e) -(CH₂)_u-CO-NR₆R₇ wherein u is as defined above, and R₆ and R₇ are as defined above;

with the proviso that compound of formula (I) is neither of 2-(4-benzyloxybenzoylamino)-3-phenylpropionic acid, 2-[4-(4-methoxybenzyloxy)benzoylamino]-3-phenylpropionic acid, 2-[4-(4-bromobenzyloxy)benzoylamino]-3-phenylpropionic

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acid, , cyclopentyl- [4-(2-methylquinolin-4-ylmethoxy)benzoylamino]acetic acid methyl ester, [4-(2-methylquinolin-4-ylmethoxy)benzoylamino] (tetrahydropyran-4-yl)acetic acid methyl ester or 2-(4-benzyloxybenzoylamino)-3-biphenyl-4-ylpropionic acid or 2-(4-benzyloxybenzoylamino)-3-(4'-trifluoromethoxybiphenyl-4-yl)propionic acid.

2. The compound according to claim 1, wherein W is -NH-CH(E) -.

3. The compound according to claim 2, wherein -Z is a radical of the -Q-I-J-T type.

4. The compound according to claim 2, wherein -Z is a radical of the $-(CH_2)_s-X-P-I-J-T$ type.

5. The compound according to claim 4, wherein -X- is -O-.

6. The compound according to claim 4, wherein s is 2 and -X- is -NR₄-.

7. The compound of claim 1, wherein W is -N(E)-CH₂-CH₂-.

8. The compound according to claim 7, wherein -Z is a radical of the -Q-I-J-T type.

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